REMARKS

Claims 60, 63, 66, 67, 71, 73-76, 78, 80, and 82-84 have been amended. New Claim 86 has been added. Support for the amendments and the new claim can be found in the Specification as filed and claims as filed. Claims 64, 65, 68-70, 72 and 85 have been cancelled without prejudice to pursue the claims to the current commercial embodiment and thus for reasons unrelated to patentability. Applicant reserves the right to pursue the subject matter of the cancelled claims in a related application. Claims 61, 62 and 77 have been cancelled as redundant. No new matter has been introduced by these amendments. The following addresses the substance of the Official Action.

Claim objection

The Examiner has objected to Claim 71 for reciting "bihenylmaleate" rather than "biphenylmaleate". Applicant has amended Claim 71 accordingly.

Definiteness

The Examiner has rejected Claim 71 under 35 USC §112, second paragraph as being indefinite. Specifically, Claim 71 includes the species of N,N-diethyl toluamide and benzoic acid, which do not conform to the structural requirements of Claim 64. Claim 71 has been amended and is now an independent claim. Therefore, currently amended claim 71 is definite and its rejection under 35 USC §112, second paragraph should be withdrawn.

Written description

The Examiner has rejected Claims 60-62, 64-70, 72-76, and 78-85 under 35 USC §112, first paragraph as allegedly not supported by the Specification as filed. Specifically, the Examiner has stated that the genus of lipophilic molecules claimed is too broad and encompasses organic molecules which have no structural similarity to the specific phthalates, maleates, succinates and fumarates taught by the specification, nor the N,N-diethyltoluamide, camphor or benzoic acid. The Examiner also stated that the genus of terpenes of Claim 72 is too broad, while the specification only discloses one species of the genus – camphor. The Examiner further stated that the genus of molecules in Claim 64 has multitude of variants, as W in formula 1, X, R3, R3', R4 and R4' can be various groups. Applicant wished to remind the Examiner, that on December 2, 2002 in response to the 3rd restriction requirement, the chemical moieties of the elected species of the structure 2 were elected as follows: X – is oxygen, R1 and R2 are alkyl side

chains comprising 4 carbon atoms, such as $(CH2)_3$-CH_3; R3 and R4 are linked to form a cyclic ring, which comprises unsaturated C_6 cycloalkyl. However, to expedite the allowance of claims directed to the present commercial embodiment, Claim 60 has been amended to recite generic structures tailored to cover the majority of the specific phthalates, maleates, succinates and fumarates taught by the specification. Claims 64, 65, 68-70, 72 and 85 have been cancelled without prejudice as discussed above, and claims 66, 67, 73-84 now depend on Claim 60. Therefore, currently amended Claims 60, 66, 67, 73-76 and 78-84 are supported by the specification as filed, and their rejection under 35 USC §112, first paragraph should be withdrawn.

Novelty

The Examiner has rejected Claims 60-62, 82 and 83 under 35 USC §102(b) as being allegedly anticipated by Daynes et al. (WO 91/04030). Specifically, the Examiner has stated that even though Daynes et al. do not teach that steroid hormones DHEA or 1,25(OH)2D3 are sufficient to increase number of dendritic cells migrating to a lymphoid organ in the absence of antigen, or increase the number of antigen-bearing dendritic cells in a lymphoid organ by a factor of 2 to 100, these molecules are lipophilic and are applied topically to the mouse skin to modulate the immune response of said mouse to an injected antigen. Therefore, the Examiner put the burden on the Applicant to prove that the claimed product is different from those taught by the cited reference.

> To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed.Cir. 1986). "[A]nticipation requires that all of the elements and limitations of the claim are found within a single prior art reference." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

DHEA or 1,25(OH)2D3 are steroids and do not fall within the chemical genera now recited in amended Claims 60, 82 and 83. Therefore, these claims are novel over Daynes et al. and their rejection under 35 USC §102(b) should be withdrawn.

The Examiner has rejected Claims 60 and 77 under 35 USC §102(b) as being allegedly anticipated by Kost et al. (WO 88/00001) as evidenced by Mitragotri et al. (WO 00/35351). Specifically, the Examiner has stated that even though Kost et al. do not disclose that the

application of ultrasound energy would cause an increase in the number of dendritic cells migrating to a lymphoid organ, it would be inherent as taught by the instant specification. Claim 77 has been cancelled, while Claim 60 now recites specific compounds that are not disclosed in Kost et al. New Claim 86 recites combining injection of an antigen with ultrasound, such method is also not disclosed in Kost et al.

For all of the above reasons, Claims 60 and 86 are novel, and their rejection under 35 USC §102(b) should be withdrawn.

Non-obviousness

The Examiner has rejected Claims 60-62, 64-70, 72-76 and 78-85 under 35 USC §103(a) as being allegedly obvious over Baumann et al. (*J. Immunol.* 2000, 165:158-167) in view of Price et al. (*J. Exp. Med.* 1997, 186:1725-1735). Specifically, the Examiner has stated that one of skill in the art would have been motivated at the time the invention was made to combine the teachings of Baumann et al. that increases in stimulatory Langerhans cells in the lymph nodes draining the site of antigen deposition are needed to induce a protective response with the teachings of Price et al. that topical exposure to chemical allergens such as oxazolone (lipophilic molecule of less than 500 Daltons) results in the migration of epidermal Langerhans cells from the skin and accumulation as immunostimulatory dendritic cells in the draining lymph nodes.

> Under MPEP §2143 "[t]o establish a *prima facie* case of obviousness... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure..."

Bauman et al. describes that a subcutaneous injection of *Cryptococcus neoformans* culture supernatant (containing soluble cryptococcal antigens) emulsified in complete Freund's adjuvant (containing Mycobacteria) results in the migration of Langerhans cells into the draining lymph node and induction of protective anti-cryptococcal immunity. Price et al. disclose in the first sentence of the Summary that "Topical exposure of mice to chemical allergens results in the migration of epidermal Langerhans cells from the skin and their accumulation as immunostimulatory dendritic cells in draining lymph nodes". Chemical allergens are antigens known as haptens.

It was well known in the art at the time this invention was made that topical application of contact allergens (haptenic antigens capable of crossing the stratum corneum) caused the migration of epidermal Langerhans cells. This is why Dearman et al. (*Fundamental and Applied Toxicology*, 1996, Vol. 33, pp. 24-30), discussed in the previous Office Action response and during the Examiner's interview on September 22, 2005, explicitly taught that it was the haptenic antigen FITC, and NOT the non-antigenic dibutylphthalate (DBP), that caused the migration of Langerhans cells to the draining lymph node. By contrast, Claim 60 recites "a topical treatment which in the absence of antigen is sufficient to increase the number of dendritic cells migrating to a lymphoid organ..." This issue was discussed at length with the Examiner during the September 22, 2005 interview. The Examiner understood the distinction and agreed to the non-obviousness of the claims over the Dearman reference.

There are several reasons why Bauman et al in view of Price et al. also do not make current claims 60, 66, 67, 73-76 and 78-84 obvious. First, like Dearman, neither Bauman et al. nor Price et al. suggest the existence of a molecule that is $\leq$ 500 daltons, that can be applied topically, and that will induce the migration of epidermal Langerhans cells to the draining lymph node in the absence of antigen. Second, both Bauman et al. and Price et al. deliver to the mammal one composition containing both an antigen and a migration inducer. Bauman injects the composition subcutaneously; Price applies skin sensitizer oxazolone topically. They never suggest that it might be possible to inject an antigen into the mammal and separately apply a migration inducer — that is not an antigen — topically, and that they would work in concert to induce an immune response to the antigen. They never mention any such concept. In fact, they never suggest that an inducer of dendritic cell migration and maturation might exist independently of an antigen. Further, amended Claim 60 now recites genera of topical inducers tailored to cover the specific phthalates, maleates, succinates and fumarates, which are taught by the specification as inducing migration in the absence of antigen. The Examiner has already acknowledged that Applicant's method reciting dibutyl phthalate as a specific inducer (Claim 63) is allowable. For the above reasons, Applicant respectfully asserts that claims 60, 66, 67, 73-76 and 78-84 are non-obvious over Bauman et al in view of Price et al., and their rejection under 35 USC §103(a) should be withdrawn.

Double patenting rejections

The Examiner has rejected Claims 60 and 77 under the judicially created doctrine of obviousness-type double patenting over claims 1-4, 7, 16-18 and 20 of US patent 6,210,672. The Examiner has rejected Claims 60-76 and 78-85 under the judicially created doctrine of obviousness-type double patenting over claims 1-15 of US patent 6,210,672.

Applicant appreciates the Examiner's acknowledgement that a terminal disclaimer will be filed at the time allowable subject matter is indicated.

Allowable subject matter

The Examiner has indicated that Claim 63 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 63 has now been amended accordingly.

CONCLUSION

Applicant has addressed all of the Examiner's concerns as expressed in the outstanding Office Communication dated March 13, 2006. If the Examiner finds any remaining impediment to the prompt allowance of the pending claims that could be clarified with a telephone conference, the Examiner is respectfully invited to call the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: July 12, 2006

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